IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

In re Application of)
MARTIN J. PAGE)
Serial No. 08/155,864)
Filed: 23rd November 1993)
For: ANTIBODY PRODUCTION)

Examiner: D. ADAMS

Group Art Unit: 1806

DECLARATION

I, GEOFFREY HALE, of The University of Cambridge, Department of Pathology, Tennis Court Road, Cambridge, CB2 1QP do hereby solemnly and sincerely declare as follows:

1. I received the degree of BA in Natural Sciences from the University of Cambridge in 1974 and the degree of PhD in Biochemistry from the same university in 1977. Since 1977 I have been engaged in research at the University of Cambridge holding the positions of research assistant (1977-1985), research associate 1985-1986 and senior research associate from 1986 to date. I am currently scientific director of the MRC/Wellcome Therapeutic Antibody Centre, Department of Pathology, University of Cambridge.

2. THE humanised anti-CDw 52 antibody CAMPATH 1H was developed by workers at the MRC Laboratory of Molecular Biology at Cambridge and the Department of Pathology at the University of Cambridge. The first clinical use of CAMPATH 1H in man was in the treatment of non-Hodgkin lymphoma and I was involved in the design of the therapeutic approach using this antibody (see Hale *et al*, The Lancet, 17th December 1988, pages 1394-1399).

2. CAMPATH 1H was produced initially by engineering a rat myeloma cell line and antibody purified from the culture of this cell line was used for the first clinical studies with the antibody. However, it was clear that for clinical trials to

continue it would be advantageous to develop cell lines which produced the antibody in larger amounts.

3. FROM about 1988, development of CAMPATH 1H was undertaken in conjunction with The Wellcome Foundation Limited and I was aware of work being carried out at Wellcome to increase the yield of CAMPATH 1H, including the engineering of a CHO cell line to produce the antibody. At this time, I was aware of the fact that the ability of an antibody to recruit effector mechanisms and the half life of an antibody in the circulation were very much affected by the glycosylation of the antibody. I was also aware of the fact that glycosylation of a protein is dependant on the cell in which that protein is produced.

4. FOR this reason, I expected that the glycosylation on CAMPATH 1H produced in CHO cells would be different from that on CAMPATH 1H produced in rat myeloma cells. Not only are CHO cells from a different species to the cells previously used to produce the antibody (hamster as opposed to rat) they are of a different type (ovary as opposed to lymphoid) and I assumed that both of these differences would have an effect on glycosylation.

5. ALTHOUGH I knew that there would be differences in glycosylation between CAMPATH 1H produced in CHO cells and the CAMPATH 1H that had been used for the initial clinical studies in man, I did not know what the effect of these differences would be. I hoped that the difference in glycosylation might be essentially neutral, i.e. the effectiveness of the antibody as a therapeutic agent would be unaffected. However, I had no expectation that this would necessarily be the case and I was very much aware of the fact that it might not be. For this reason, I was very pleased and even relieved when the first results that were obtained from the clinical use of CAMPATH 1H produced from CHO cells showed that the antibody produced in this way was as effective therapeutically as antibody produced in rat myeloma cells.

6. AT the time that the first results on CAMPATH 1H produced in CHO cells were obtained, I was in charge of the MRC/Wellcome Therapeutic Antibody Centre at Cambridge, one function of which was to produce antibodies in sufficient quantities for clinical studies. In a Progress Report written at the end of 1990 I referred to the first successful use in man of CAMPATH 1H produced in CHO cells and I made the following comment:

> *"This result was very important to us because the CAMPATH 1H had been produced in CHO (chinese hamster ovary) cells rather that the rat myeloma cells as before. The CHO cells offer increased productivity and so are being used by Wellcome and by us for most future antibodies. However, there had been some doubt whether the antibody produced would be as effective in vivo. Therefore the successful treatment of this first patient has been very encouraging to all of us."*

The reasons for the doubt that I referred to in this report at the end of 1990 are those that I have already explained above relating to the potential for the different glycosylation of an antibody produced in CHO cells to have an adverse effect on the ability of the antibody to recruit effector mechanisms and on the half life of the antibody in the circulation.

7. I further declare that all statements made herein to my knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statement and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.

Geoffrey Hale

GEOFFREY HALE

Date: 16 November 1994